A Randomized Trial to Compare Percutaneous Coronary Intervention Between Massachusetts Hospitals With Cardiac Surgery-On-Site and Community Hospitals Without Cardiac Surgery-On-Site

The MASS COMM Trial

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PROTOCOL SUMMARY

Title: A randomized trial to compare percutaneous coronary intervention between Massachusetts hospitals with cardiac surgery-on-site and community hospitals without cardiac surgery-on-site

Objective: The primary objective of the trial is to compare the acute safety and long term outcomes between hospitals with cardiac surgery on-site (SOS hospitals) and hospitals without cardiac surgery on-site (non-SOS hospitals) for patients with ischemic heart disease treated by elective PCI (stable angina, acute coronary syndrome, or non-Q MI).

Design: The MASS COMM trial is a prospective, multi-center, nested randomized controlled two-arm trial of PCI performed at non-SOS hospitals (non-SOS-PCI arm) versus PCI performed at SOS hospitals (SOS-PCI arm). The trial is designed to show non-inferiority of the non-SOS-PCI arm to the SOS-PCI arm, assuming an expected 30-day adverse event rate of 4.0%, and a 12 month adverse event rate of 10%, for the base case SOS-PCI arm. The trial will have a 2.5% one-sided type I error and 90% power to detect a 2.0% difference in 30-day rates, and 3.0% difference in 12 month rates, differences, which if exceeded by the non-SOS-PCI arm will fail to reject the null hypothesis of inferiority.

Specifically, 6000 subjects will be enrolled in a multicenter nested RCT, in which 4800 eligible subjects will be consented and randomized in a 3:1 ratio at the non-SOS hospitals for PCI to be performed at either the enrolling non-SOS hospital (3 chances out of 4) or a corresponding SOS hospital (1 chance out of 4). The "nested" portion of the RCT refers to an additional 1200 subjects who will be randomly chosen (then consented) from the patient pool undergoing routine PCI at the SOS hospitals, and who meet the eligibility criteria for the MASS COMM trial. An angiographic subset will be reviewed by an independent committee to assess appropriateness and completeness of revascularization. The subset will include the first 10% of subjects consecutively enrolled at all study sites enrolling subjects in both randomized and nested portions of the trial.

Primary Endpoints: The primary safety endpoint is 30-day major adverse cardiac event (MACE) rate, defined as a composite endpoint of the occurrence of either all cause mortality, target vessel myocardial infarction (Q wave and non-Q wave), repeat coronary

revascularization (of the target vessel or non-target vessel) by either percutaneous or coronary artery bypass graft [CABG] methods, or stroke, at 30-days. In the case of patients presenting with non-ST elevation myocardial infarction, for the purposes of the primary and other endpoints, myocardial infarction will be defined as re-infarction following the PCI.

The primary efficacy endpoint is the 12 month rate of MACE, defined as a composite endpoint of the occurrence of either all cause mortality, target vessel myocardial infarction (Q wave and non-Q wave), repeat coronary revascularization (of the target vessel or non-target vessel) by either percutaneous or coronary artery bypass graft [CABG] methods, or stroke, at 12 months.

Secondary Endpoints:

1. All cause mortality at 30 days and 12 months.
2. Rate of stroke at 30 days and 12 months.
3. Ischemia-driven TLR and TVR at 12 months.
4. Any revascularization at 12 months.
5. Rate of urgent revascularization through day 30.
6. Procedure success defined as lesion success without the occurrence of in-hospital MACE.
7. Major vascular complications including access site complications and major bleeding events requiring transfusion at 30 days.
8. Completeness of revascularization defined as proportion of epicardial vessels with >70% and <100% stenosis treated with procedural success (assessed in an angiographic subset of patients).
9. Appropriateness of revascularization defined as the proportion of lesions meeting ACC Class I and II guidelines (assessed in an angiographic subset of patients).

Enrollment: 6000 subjects will be enrolled from approximately 14 MA clinical study sites throughout Massachusetts.
NOTE: Additional sites will be considered according to diagnostic and primary PCI case volume as specified by the Massachusetts Department of Public Health (MA-DPH).

Timeline: Enrollment will begin in June 2006

Study Population: Subjects with ischemic heart disease due to stenotic lesions of native coronary arteries amenable to coronary stenting with FDA-approved coronary stents (both bare metal stents [BMS] and drug eluting stents [DES] are permitted).

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STUDY SITES:	**NON-SURGERY ON SITE (NON-SOS) HOSPITALS*** Caritas Norwood Hospital Brockton Hospital Lowell General Hospital Melrose Wakefield Metrowest Medical Center Saints Memorial Medical Center South Shore Hospital **SURGERY ON SITE (SOS) HOSPITALS** Beth Israel Deaconess Medical Center Boston University Medical Center Brigham and Women's Hospital Lahey Clinic Massachusetts General Hospital New England Medical Center St Elizabeth's Hospital

** Participation of non-SOS sites is contingent upon approval by the Massachusetts Department of Public Health (MA-DPH). Additional sites may be added upon approval of diagnostic and primary PCI case volume as specified by the MA-DPH.*

1.0 BACKGROUND AND INTRODUCTION

Introduction
Progress in percutaneous coronary interventions (PCI) has resulted in lower restenosis rates and lower emergency cardiac surgical rescue rates. This improvement in the field has prompted the consideration of moving from the traditional platform of elective PCI at tertiary hospitals with cardiac surgery on site (SOS) to community hospitals without cardiac surgical back-up (non-SOS). The reasons for such consideration are based on the perception of improved convenience due to reduced travel time for the patient, friends, and family, and continuous local involvement of the patient's physicians. In the Commonwealth of Massachusetts, there are no non-SOS hospitals performing elective PCI, although several such hospitals are performing PCI for acute ST-elevation myocardial infarction (STEMI), under the supervision of the Department of Public Health in the Commonwealth of Massachusetts.

PCI for Non-AMI Coronary Ischemia at Hospitals Without Surgical Back-up
The consideration of performing PCI at hospitals without on-site cardiac surgery has been best studied in the setting of acute coronary syndromes. Compared with medical therapy, randomized trials have shown a benefit from early percutaneous coronary interventions (PCI) in acute coronary syndromes, both for acute myocardial infarction (STEMI)[1-3] and acute coronary syndromes (unstable angina)[4]. This utility of PCI was based on standard PCI programs of skilled operators and experienced hospital staffs at hospitals with cardiac surgical back-up. These benefit of PCI over medical therapy in acute coronary syndromes at SOS hospital helped to establish the basis for evaluation of PCI at hospitals without on-site cardiac surgery. The potential incremental value of PCI performed at hospitals with cardiac surgery over those without cardiac surgery, however, may not be limited to the availability of cardiac surgery alone. Hospitals with cardiac surgery programs may also have larger and more complete revascularization services, with greater staff experience, compared with those hospitals without cardiac surgical services[5].

Two implicit comparisons are required to evaluate the consideration of instituting PCI for non-acute MI coronary ischemia at hospitals without cardiac surgery: 1) comparison of outcomes of acute coronary syndromes, including AMI, between PCI (at hospitals without cardiac surgery) and medical therapy, and 2) comparison of non-STEMI PCI outcomes between hospitals with and without cardiac surgery. The first comparisons have been performed retrospectively and prospectively, while the second comparisons have not been performed directly.

The benefit seen from PCI for STEMI (compared with thrombolytic therapy) demonstrated from multicenter randomized trials involving hospitals with cardiac surgery[1], has been seen also in studies from hospitals without cardiac surgery[6-10]. While several of these studies were based on the use of skilled personnel staff from hospitals with elective PCI programs with cardiac surgery, the data suggests that skilled and experienced operators and supportive staff are required, as well as a transportation

system that facilitates rapid transfer to a facility that can perform surgical revascularization, if needed. A minority of thought leaders still raise concerns about the wisdom of performing primary PCI for acute MI at hospitals without cardiac surgery[11,12].

There have, however, been no direct randomized trial data comparing PCI for acute MI at hospitals with cardiac surgery versus hospitals without cardiac surgery. The conclusions made that support PCI for acute MI at hospitals without cardiac surgery are based on observational outcome data and the single randomized trial, Atlantic C-PORT[10]. The 551 patient C-PORT trial, which compared thrombolysis to PCI for the treatment of acute ST-segment elevation MI at hospitals without cardiac surgery, demonstrated a lower incidence of the composite endpoint of death, recurrent MI, and stroke. The difference in the composite endpoint, between PCI versus thrombolysis (16.8% vs. 9.8%), was not driven by death (5.3% vs. 6.2%), but rather by reduced stroke (1.3% vs. 3.5%) and recurrent MI (4.0% vs. 8.8%). These component endpoint reductions are rationally predictable for PCI, since the avoidance of thrombolysis reduces stroke, and the intervention of the index lesion has been shown to reduce recurrent MI[1,2].

The need for emergent or urgent cardiac surgery services in patients who undergo primary PCI is evident. The randomized 1100 patient multicenter PAMI-2 trial of PCI for acute MI at hospitals with cardiac surgery employed cardiac surgical revascularization during the acute MI index hospitalization in 11% of patients[13]. Surgery within 24 hours was required in 2.5%, and emergent surgery for failed PCI in 0.4%.

A comparison of mortality outcomes in randomized trials comparing PCI with thrombolysis for acute MI in the U.S. and the Netherlands (adopted from Aversano[10]), shows a trend for a larger difference in mortality in studies at hospitals with cardiac surgery (Table 1). A direct comparison with hospitals that have cardiac surgery could be enlightening.

Table 1. Death rates by PCI versus thrombolysis, stratified by availability of cardiac surgery in hospital (adopted from Aversano et al).

	No Cardiac Surgery	**Cardiac Surgery**		
	C-PORT	**Weaver**	**PAMI**	**Zijlstra**
Primary PCI	5.3%	4.4%	2.6%	0%
Thrombolysis	7.1%	6.5%	6.5%	6.0%

The benefit of PCI over medical therapy for patients with acute MI can also be realized by employing a transportation strategy from community hospitals without cardiac surgery to tertiary centers with cardiac surgery. The DANAMI-2 randomized trial demonstrated that PCI for acute MI after transport from a community hospital without PCI capability to a tertiary medical center with PCI capability and cardiac surgical back-up(within 2 hours), was superior to community hospital dispensed thrombolysis[14].

Feasibility of Elective PCI Without Surgical Back-up

The utility of elective PCI at hospitals without cardiac surgery is based on the early and definitive coronary treatment element of PCI over medical therapy for STEMI. Performing elective PCI at hospitals without cardiac surgery remains controversial and has not been well studied. The existing PCI guidelines, written by the American College of Cardiology and American Heart Association Task Force, thus recommend that elective PCI to be performed only at hospitals with on-site cardiac surgical back-up[15].

Few reports have been published that support the utility of elective PCI at hospitals without on-site cardiac surgery, in the current era of glycoprotein IIb/IIIa inhibitors and stents[16-18]. The reports at hospitals without cardiac surgery summarize retrospective or registry prospective studies, with sample sizes that range from 196 to 506 patients. All studies utilized: 1) restricted criteria for patient and lesion complexity, 2) experienced operators from hospitals with cardiac surgery (and in one study, mandatory on-line video consultation with a tertiary hospital). There currently exists no randomized data, nor a sufficient sample size in any of the observational data, to assess the risk of emergent bypass surgery or death complications with precision less than 2%, the current rate of emergent bypass surgery at hospitals that perform PCI with on-site cardiac surgery.

Given the unpredictable risk of even a rare patient who may need immediate surgical attention in order to save his/her life, the rationale for unrestricted PCI without on-site surgical back-up is not without its detractors. Correlation of high volume and experienced PCI operators and support staff with hospitals that have cardiac surgery with outcomes has also been proposed as a factor for consideration of not adopting a community hospital-based PCI strategy[19].

Motivation for Proposed Study

If there is a compelling need to perform PCI in Massachusetts at community hospitals without cardiac surgery, a study should be commissioned, at the very least. The study should involve comparison of complications and late-term revascularization, including the need for emergency surgery, between tertiary (SOS) and community (non-SOS) hospitals.

2.0 STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the trial is to compare the acute safety and long-term outcomes for patients with myocardial ischemia (other than ST-segment elevation myocardial infarction [STEMI]) who are treated by PCI at hospitals without cardiac surgery-on-site (*non-SOS hospitals*) to patients treated at hospitals with cardiac surgery-on-site (*SOS hospitals*). The comparators will be measured as rates of complications (both acute and late-term) and ischemia-driven need for subsequent coronary revascularization in either the target vessels or non-target vessels. This analysis will thus attempt to compare the safety and efficacy of PCI, and either accept or reject the null-hypothesis that PCI performed at non-SOS is inferior to that performed at SOS hospitals.

2.1.1 Primary Endpoint

The primary endpoint of this trial will be measured at 30 days (safety) and 12 month (efficacy). The primary endpoint is defined a composite endpoint of the occurrence of death (from all cause), target vessel myocardial infarction, repeat coronary revascularization, or stroke.

2.2. SECONDARY OBJECTIVES

Once the above primary objectives are established, secondary analyses must support patient safety at all levels of potential morbidity.

2.2.1 Secondary Endpoints

The secondary endpoints include both safety and efficacy measures and are as follows:

1. All cause mortality at 30 days and 12 months.
2. Stroke at 30 days and 12 months.
3. Ischemia driven TLR and TVR at 12 months.
4. Any coronary revascularization through month 12. Revascularization will be categorized according to relatedness to the target lesion or target vessel (e.g., as either target lesion or target vessel related or non-target lesion or non-target vessel related).
5. Rate of urgent revascularization through day 30.
6. Procedure success defined as lesion success without the occurrence of in-hospital MACE.
7. Major vascular complications, including access site complications and major bleeding events requiring transfusions, through day 30.
8. Completeness of revascularization, defined as proportion of epicardial vessels with >70% and <100% stenosis treated with procedural success.

9. Appropriateness of revascularization, defined as the proportion of lesions meeting Class I and II criteria per the 2005 Angioplasty Guidelines of AHA/ACC/SCAI or subsequent modifications thereof.

3.0. STUDY DESIGN

The MASS COMM trial is a prospective, multi-center, nested randomized controlled two-arm trial of PCI performed at non-SOS hospitals (non-SOS-PCI arm) versus PCI performed at SOS hospitals (SOS-PCI arm). The trial is designed to reject the null-hypothesis of inferiority, and thereby show the non-inferiority of the non-SOS-PCI arm to the SOS-PCI arm. Assuming an expected 30-day major adverse cardiac event rate of 4.0%, and a 12 month major adverse cardiac event rate of 10%, for the base case SOS-PCI arm, the trial will have a 2.5% one-sided type I error and 90% power to detect a 2.0% difference in 30-day rates, and 3.0% difference in 12 month rates, differences. If these difference boundaries are exceeded by the non-SOS-PCI arm, the trial will fail to reject the null hypothesis of inferiority.

Specifically, 6000 subjects will be enrolled in a multi-center nested RCT, in which 4800 eligible subjects will be consented and randomized in a 3:1 ratio at the non-SOS hospitals for PCI to be performed at either the enrolling non-SOS hospital (3 chances out of 4) or a corresponding SOS hospital (1 chance out of 4). The "nested" portion of the RCT refers to an additional 1200 subjects who will be randomly chosen (then consented) from the patient pool undergoing routine PCI at the SOS hospitals, and who meet the eligibility criteria for the MASS COMM trial. This nested cohort will supplement the patients from the non-SOS hospitals randomized to undergo PCI at the SOS facilities, providing additional statistical power.

Subjects must meet eligibility criteria and agree to participate in the study, including willingness to be randomized and transported or rescheduled for treatment at a SOS hospital with on-site cardiac surgery. Subjects in the nested portion of the study must consent to data collection and follow-up visits at 30 days and 12 months only. The safety and effectiveness of PCI performed in each clinical setting will be evaluated by analyzing all clinical endpoints, ECG data, a subset of angiographic data and MACE. All subjects will undergo clinical assessments at 30 days, and 12 months.

An adjudication process will be conducted by an independent Clinical Events Committee to determine the occurrence of clinical study endpoints (MACE, procedure success, major vascular complications and appropriateness and completeness of revascularization in a subset of subjects, per the ACC/AHA/SCAI 2005 Guideline update for Percutaneous Coronary Intervention provided in the Manual of Operations) for the duration of the study. The clinical events committee (CEC) will be blinded to the assigned treatment (PCI setting) arm for the entire study. In addition, an angiographic subset will be reviewed by the independent CEC to assess appropriateness and completeness of revascularization. The subset will include the first 10% of subjects consecutively

enrolled at all study sites enrolling subjects in both randomized and nested portions of the trial.

Participating non-SOS hospitals are responsible for ensuring appropriate and safe enrollment of subjects. For sites that do not already provide primary angioplasty medical coverage on a daily basis throughout the day (e.g., 24/7), a medical team must be available and on –call to deal with complications that result from the procedure. Any patient at a non-SOS site who consents to participate in the MASS COMM trial on a day where there is no 24 hour post-procedure interventional team coverage at the non-SOS site cannot be randomized that day. Participating non-SOS hospitals are responsible for ensuring systems and processes are in place with SOS and partnering hospitals for surgical support for (1) transport and or efficient scheduling of subjects randomized to SOS PCI arm and (2) efficient and rapid transport for subjects in whom a procedural complication warrants surgical intervention.

In the case of subjects randomized to SOS PCI, every effort must be made for same day transfer and scheduling of PCI at SOS site with subject's non-SOS provider, and that such delayed PCI will be performed no later than 3 days from randomization.

For subjects requiring urgent surgical intervention due to non-SOS PCI procedural complication, the non-SOS hospital must transport the study subject to the SOS partnering hospital providing cardiac surgical support. Transport will require rapid and efficient transfer, specifically: availability of ambulance transport must arrive at non-SOS hospital within 30 minutes of request by catheterization staff due to procedural complication. Every effort must be made to ensure arrival of subject at partnering surgical hospital within 60 minutes of decision to transport study subject.

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria

Candidates for this study must meet **ALL** of the following criteria:

1. Subject is ≥ 18 years old.
2. Subject requires single- or multi-vessel percutaneous coronary intervention (PCI) of *de novo* target lesion(s).
3. Subject's lesion(s) is (are) amenable to stent treatment with currently available FDA-approved bare metal and drug eluting stents.
4. Subject is an acceptable candidate for CABG.
5. Subject has clinical evidence of ischemic heart disease in terms of a positive functional study, or documented accelerated symptoms.

6. Documented stable angina pectoris [Canadian Cardiovascular Society Classification (CCS) 1, 2, 3, or 4], unstable angina pectoris with documented ischemia (Braunwald Class IB-C, IIB-C, or IIIB-C), non-ST segment elevation myocardial infarction*, or documented silent ischemia.

   *Note: Subjects with non-ST segment elevation myocardial infarction may be enrolled if 2 or more CK-MB blood results show a decrease in CK-MB below the site's upper limit of normal or to below half of its peak level.

7. Subject is willing and able to undergo percutaneous intervention at SOS hospital, if randomized to SOS study arm.
8. Subject and the treating physician agree that the subject will comply with all follow-up evaluations.
9. Subject has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board/Ethics Committee of the respective clinical site

Angiographic Inclusion Criteria

10. The target lesion(s) is (are) *de novo* native coronary artery lesion(s) with ≥50 and <100% stenosis (visual estimate), or the target lesion is an acute (less than 1 month) total occlusion as evidenced by clinical symptoms.

3.1.2. Exclusion Criteria

Subjects will be excluded if **ANY** of the following conditions apply:

1. The patient is pregnant or breastfeeding.
2. Evidence of ST segment elevation myocardial infarction within 48 hours of the intended treatment.
3. Cardiogenic shock on presentation or during current hospitalization.
4. Left ventricular ejection fraction less than 20% (LVEF test result performed 30 days prior to randomization can qualify the patient for randomization).
5. Known allergies to: aspirin, clopidogrel (Plavix®) and ticlopidine (Ticlid®), heparin, bivalirudin, stainless steel, or contrast agent (which cannot be cannot be adequately premedicated).

6. A platelet count <75,000 cells/mm^3 or >700,000 cells/mm^3 or a WBC <3,000 cells/mm^3.
7. Acute or chronic renal dysfunction (creatinine >2.5 mg/dl or >150µmol/L).
8. Subject is currently participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints. (Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials).
9. Prior participation in this study.
10. Within 30 days prior to the index study procedure, the subject has undergone a previous coronary interventional procedure of any kind.
11. Stroke or transient ischemic attack within the prior 3 months.
12. Active peptic ulcer or upper GI bleeding within the prior 3 months.
13. Subject has active sepsis.
14. Unprotected left main coronary artery disease (stenosis >50%).
15. In the investigator's opinion, subject has a co-morbid condition(s) that could limit the life expectancy to less than one year, or limit the subject's ability to participate in the study or comply with follow-up requirements or impact the scientific integrity of the study.

Angiographic Exclusion Criteria

16. The target vessel is associated with ST-segment elevation MI.
17. Any target vessel has evidence of excessive thrombus (e.g. requires target vessel thrombectomy) or tortuousity (>60 degree angle) that makes it unsuitable for proper stent delivery and deployment.
18. Any target lesion requires treatment with a device other than PTCA prior to stent placement (e.g. but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
19. Any lesion is located in a saphenous vein graft.

20. The target vessel is in a "last remaining" epicardial vessel (e.g. >2 non-target epicardial vessels and the bypass grafts to these territories [if present] are totally occluded).

Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled into the study.

3.2 INFORMED CONSENT AND SUBJECT RECRUITMENT

Subjects recruited for randomization at non-SOS hospitals will sign a consent form describing the study purpose and full study procedures, risks, specifically the investigational nature of PCI performed at hospitals with no surgery on site, and discomforts (including need for transport or delayed scheduling of procedure to be performed at participating SOS hospital) as well as benefits. Subjects participating in the nested control group at a SOS hospital will sign a separate informed consent document describing the overall study and its purpose, but the description of study procedures will reflect the limited study requirements of this group, and that study requirements will be limited to permission for data collection for procedure-related, 30 day and 12 month outcomes.

A member of the each study site research team (catheterization lab nurses, fellows or physicians) will approach the patient to obtain written informed consent prior to any screening or interventional procedure being performed. The background of the proposed study and the benefits and risks of the procedures and study should be explained to the patient. The patient (or legal representative) must sign the consent form prior to randomization. This form or a modification of it must have prior approval of the study site's Institutional Review Board (IRB). Failure to provide informed consent renders the patient ineligible for study participation and data collection.

Subject screening and eligibility will be documented on the *Subject Screening and Eligibility Log* for all subjects who sign informed consent. Research personnel at each site will record the criteria by which subjects are excluded or will record the date of subject enrollment. Adult patients will be enrolled without regard to age or sex and will be included or excluded from enrollment based upon the inclusion and exclusion criteria listed above.

3.3 RANDOMIZATION

Subjects will be randomized after it has been determined that the subject meets all medical and angiographic eligibility criteria. For subjects recruited at non-SOS hospital locations, randomization may require either ambulance transport to the appropriate SOS participating hospital for PCI procedure (for subjects in whom removing sheath access is not practical) or subjects may be scheduled for their assigned procedure at the SOS hospital with their community provider later the same day (no subject should be delayed more than 3 days for assigned SOS PCI). Randomization will occur through the use of sealed envelopes located in the cardiac catheterization laboratory (excluding subjects

enrolled in the nested study cohort). The randomization of subjects will be stratified based upon diabetic status (presence or absence).

4.0 STUDY PROCEDURES

4.1 PRE-PROCEDURE

All candidates for study entry should be screened for eligibility. Prior to any study-specific tests or procedures, written informed consent must be obtained from the subject.

4.2 BASELINE PROCEDURES

The following tests and procedures must be performed prior to the index procedure to verify eligibility:

- Physical examination and relevant cardiac medical history including angina status or myocardial ischemia assessment, patient demographic information and cardiac risk factor history *(may be performed within 7 days prior to the index procedure);*
- Routine laboratory tests including complete blood count (CBC), platelet count, and serum creatinine obtained within 7 days prior to the index procedure;
- Baseline cardiac enzymes (CK), isoenzymes CK-MB obtained within 24 hours of the index procedure;
- A 12-lead electrocardiogram obtained within 7 days prior to the procedure, for subjects scheduled for elective PCI. Subjects with ischemic symptoms suggestive of a possible MI in evolution must have a 12 lead ECG within 24 hours prior to randomization.
- Assessment of left ventricular function by echocardiography or left ventriculography within 30 days of the procedure.
- Reference vessel characteristics (diameter, tortuosity) and lesion characteristics (CASS site, lesion length, calcification, lesion pre-treatments performed, pre- and post- TIMI flow, lesion classification) will be collected on eCRF.
- Procedural information to be collected include: procedure start and stop time, volume of contrast, devices used, peri-procedural complications (including final dissection, if any) and achievement of procedural success.

4.3 CONCOMITANT MEDICATIONS

It is strongly recommended that all subjects receive the medication regimen listed below. All medications administered should be recorded in the subject's medical record. The use of procedural medications (heparin, GPIIb/IIIa receptor inhibitors, etc) must be captured and reported. Anti-platelet and anti-coagulant medication taken by the subject (e.g., ASA, Plavix, Ticlid), including dosage, must be reported on the eCRF throughout the duration of the trial.

TABLE 2. Concomitant Medications

Timing	Medication	Procedure
Prior to Stent Implant	IV Heparin or bivalirudin	Per routine hospital practice
	Aspirin	At least 325 mg QD
	Clopidogrel[a,b]	300-600 mg loading dose
During Procedure	IV Heparin or bivalirudin	Per routine hospital practice
	IIb/IIIa Inhibitor	Per clinical judgment
	Intracoronary Nitroglycerin	50-200 mcg *prior to baseline* and post intervention angiograms;
Post-Procedure	IV Heparin or bivalirudin	Maintenance dose per routine hospital practice
	IIb/IIIa Inhibitor	Maintenance dose per routine hospital practice
	Aspirin	325 mg QD for at least 12 months, unless documented medical reason for not continuing at this dose.
	Clopidogrel[a]	75 mg po QD (for 3-6 months)

a Investigator may substitute ticlopidine for subjects who are allergic or sensitive to clopidogrel, Subjects on ticlopidine are to have CBCs performed per the drug labeling. Minimum duration per indications for use for stent (1 month for bare metal, 3 months for Cypher, 6 months for Taxus). Clopidogrel may be continued beyond minimum duration per clinical judgment.

b No additional loading dose is to be given to subjects who have been receiving clopidogrel ≥48 hours prior to the procedure.

4.4 STENTING PROCEDURE

4.4.1. Stent Implant Procedure

The stent implant procedure will be performed in accordance with the device Instructions for Use (IFU). Research catheterization staff must take care in their use of FDA-approved devices only.

The appropriate stent size for the target lesion will be selected (≥ 4 mm longer than the lesion length). The selected stent should be long enough to cover the lesion and pre-dilated area completely. Using the balloon markers that bracket the stent, the delivery

system will be advanced over the guidewire until the ends of the stent bracket the target lesion. Stent position will be confirmed by angiography.

Post-dilatation may be performed at the operator's discretion. The post-dilatation technique must be carefully performed to avoid balloon injury to ANY segment of the vessel that will not be entirely covered by the stent. The length of the post-dilatation balloon must be less than the total stent length that has been implanted.

The stent must be fully deployed to normal reference vessel diameter (RVD) on each side to ensure complete apposition. Optimal stent expansion requires that the stent be in full contact with the arterial wall. Do not leave any injured area uncovered by a study stent. If post dilatation is required for optimal stent placement, post dilate carefully with a balloon shorter than the segment covered by the study stent. Limit post dilatation to within the boundaries of the stent.

Upon completion of treatment for each lesion, intracoronary injection of nitroglycerin (NTG) must be administered and final angiography of the vessel performed in the two near-orthogonal views that were taken at baseline, showing each target lesion free of foreshortening or vessel overlap, using a 6 French or larger guiding catheter.

4.4.2. Bailout or Incomplete Coverage Procedures

If the patient experiences a major dissection or an occlusive complication manifested as decreased target vessel flow, chest pain or ischemic electrocardiogram (ECG) changes that do not respond to repeat balloon inflations or intracoronary vasodilators (NTG, verapamil, diltiazem), or in cases of incomplete lesion coverage, other bailout procedures may be performed, which may include additional stent placement.

If more than one stent is needed to cover the lesion completely, the stents must overlap by 2-3 mm. Stent length will be counted as described on its product label; overlap does not constitute a reduction of total stent length.

4.5 POST PROCEDURE

The procedure is considered complete after final angiographic recording of the treatment area, and once the guiding catheter has been removed from the subject. Thereafter, if a guiding catheter is re-introduced, this is considered a repeat intervention, which must be documented.

Immediately following the procedure:

- Heparin or bivalirudin should be continued or discontinued, per hospital standard
- ACT should be monitored per hospital standards
- Vascular sheaths should be removed per hospital standards
- Approved vascular closure devices may be used at the discretion of the investigator

4.6. LABORATORY AND ECG ASSESSMENTS THROUGH DISCHARGE

IMPORTANT: The tests outlined below must be performed whether or not they are considered part of the Investigator's standard of clinical practice.

A 12-lead ECG will be performed pre-procedure, prior to hospital discharge and at both the 30 day and 12 month follow up visits. Additional ECG recordings must be obtained with any suspicious ischemic episode.

Cardiac enzymes, CK and CK-MB, are to be measured at three time points: post procedure, within 6-8, 12-16, and 20-24 hours post-index procedure or prior to hospital discharge, whichever comes first.

NOTE: If the first two consecutive CK and CK-MB measurements are both normal (e.g. no elevation is observed), the third enzyme measurement is not required. Missing enzyme values due to two consecutive and normal test results, or due to patient's early discharge home prior to the third timeframe blood draw, are not deemed protocol violations.

Hospital discharge data collection will include eCRF documentation of all in-hospital cardiac-related complications and events (MI, repeat interventions, change in angina status, or stroke), peak creatinine, bleeding complications (including access site complications) and occurrence of death.

4.7 POST PROCEDURE FOLLOW-UP EVALUATIONS

All study subjects will be followed through hospital discharge and will undergo follow-up evaluations at the following time points:

4.7.1 Thirty-day Follow-up *(Clinic*):*

Study subject follow-up clinic evaluation must occur at 30-days (+ 7 days) post-procedure. The assessment will consist of:

- Angina status (according to the Canadian Cardiovascular Society Classification of angina),
- Study endpoint events of death, MI, stroke and bleeding complications,
- Concomitant anti-platelet/anti-coagulant medications
- Any interventional treatment that occurred since the previous contact (*e.g.*, repeat revascularization). This will include documentation regarding subject need for revascularization based upon clinical status, and
- 12- lead ECG.

* Clinical visit can be with physician or Research Coordinator.

4.7.2 Twelve Months Post-Procedure (*Clinic**):

A clinic visit will occur at 12 months (±30 days) post-procedure and will consist of:

- Angina status assessment (according to the Canadian Cardiovascular Society Classification of angina),
- Study endpoint events of death, MI, and stroke,
- Concomitant anti-platelet/anti-coagulant medications
- Any interventional treatment that occurred since the previous contact (*e.g.*, repeat revascularization by percutaneous or surgical methods). This will include documentation regarding subject need for revascularization based upon clinical status and
- 12- lead ECG.

* Clinical visit can be with physician or Research Coordinator.

4.7.3. Additional Angiography and Revascularization

All subsequent angiograms or revascularizations performed on the target vessel during the 12 month follow-up period should be preceded by a physician evaluation during which the physician will indicate whether or not the subject's clinical status warrants revascularization. Results of the angiograms and catheterization reports along with case report form data will be used in the adjudication of the study endpoints.

In some cases, recurrent ischemia may develop less than 30 days after successful stent placement. If angiography demonstrates a significant stenosis or sub-acute thrombotic occlusion of the target vessel, the subject will be considered an acute failure, and will continue to be included in the follow-up analyses that measure restenosis. In this situation, recurrent ischemia will be attributed to sub-acute closure, rather than restenosis.

Table 3. Schedule of Events

Schedule of Events	Pre-Procedure (Within 7 days)	Procedure	Post-Procedure	Discharge (No more than 12 hours prior)	30 Days (+ 7 days) Follow-Up Visit	12 Months (± 30 days) to End of Study Follow-Up Visit
					Clinic	Clinic
Determine Eligibility	X	X[1]				
Obtain Informed Consent	X					
Demographic Information	X					
Medical and Cardiac History	X					
Angina Status	X			X	X	X
CBC with differential and chemistry panel	X			X		
Cardiac Enzymes, CK, CK-MB	X (within 12 hours)		X (@ 6-8, 12-16, 20-24 hours[3])			
12 Lead ECG	X (within 7 days)			X	X	X
ACT		X				
Angiography and Randomization		X[2]				
Revascularization procedure(s)		X				
PCI related medications (procedural, anti-platelet/anti-thrombin, & anti-coagulants)		X		X	X	X
Study Endpoint Assessment		X		X	X	X

[1] ECG performed within 7 days prior to randomization may be used to qualify the patient for subjects undergoing elective PCI and for subjects without signs and symptoms of an MI in evolution. Subjects with ischemic symptoms suggestive of a possible MI in evolution must have a 12 lead ECG within 24 hours prior to randomization.

[2] Final eligibility and randomization is based upon angiographic eligibility criteria.

[3] If the first two consecutive CK and CK-MB measurements are both normal (e.g. no elevation is observed), the third enzyme measurement is not required. Missing enzyme values due to two consecutive and normal test results, or due to patient's early discharge home prior to the third timeframe blood draw, are not deemed protocol violations.

4.8 TRANSPORT FOR SURGICAL INTERVENTION

Subjects in whom a procedural complication warrants surgical intervention will be transported to the SOS partnering hospital providing cardiac surgical support. Transport will require rapid and efficient transfer, specifically, ambulance transport must be on site or arrive on-site at the non-SOS hospital within 30 minutes of request by catheterization staff due to procedural complication. Every effort must be made to ensure arrival of subject at partnering surgical hospital within 60 minutes of decision to transport study subject.

Data collection in the instance of urgent surgical intervention requires that the time of procedural complication, request for ambulance transport, arrival at surgical hospital and time of surgical intervention be recorded. Every effort must be made to ensure that surgical intervention begins within 120 minutes of procedural complication and interventionalist's decision to transport for emergency surgical intervention.

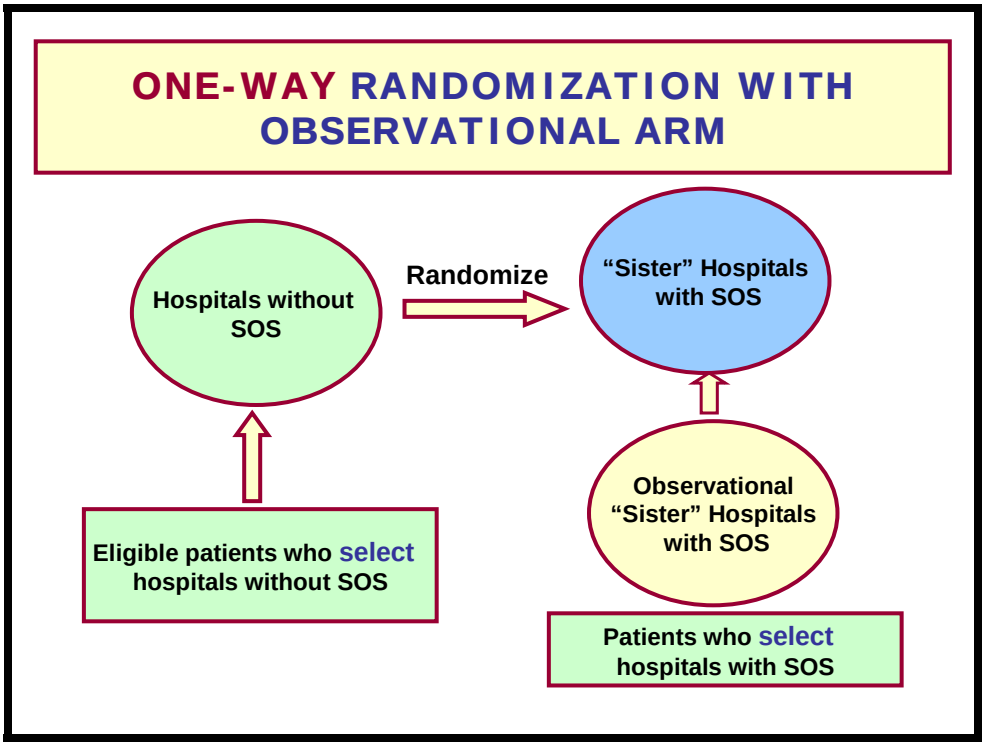
4.9 STUDY TERMINATION

MA-DPH may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All patients already enrolled will continue to be followed for the planned course of study described in this protocol. The study will be terminated following the final follow-up visit of the last enrolled patient.

5.0 STATISTICAL DESIGN

5.1 OVERVIEW

The design is a one-way randomized trial with an observational arm from which a subset of patients for the SOS arm will be borrowed. There are therefore three groups of patients: 3600 randomized to hospitals without SOS (non-SOS), 1200 randomized to hospitals with SOS, and 1200 observed (and not randomized) to hospitals with SOS. The subgroup of patients who participate in the observational SOS arm will meet the inclusion and exclusion criteria of those in the randomized arms. The ideas behind the adoption of this design are to boost external validity and to reduce overall trial costs.



KEY ASSUMPTIONS:

1. Data collection instruments are identical in the three sub-groups.
2. Schedule of data collection is identical across the three sub-groups.
3. Patients in the observational SOS arm are selected using the same inclusion and exclusion criteria as the randomized patients.
4. Because of lack of randomization, there will be differences between average outcomes in the "observational" SOS arm and average outcomes in the randomized "SOS" arm. In particular, let $y_{NON\text{-}SOS}$ denote the endpoint for patients randomized to hospitals without SOS; y_{SOS} denote the endpoint for patients randomized to hospitals with SOS; and y^{*}_{SOS} denote the endpoint for

patients who select SOS hospitals and participate in the study. The underlying assumptions are:

Analytical Assumptions for Hybrid Design. The factor by which the observational SOS arm over- or under-estimates the average outcomes in the randomized SOS arm is σ_0. SOS = surgery on site. Outcome = All cause mortality, MI, repeat coronary revascularization, or stroke.		
Hospital Type	**NON-SOS**	**SOS**
Randomized	Mean: $\mu_{NON\text{-}SOS}$ Variance: $\sigma^2_{NON\text{-}SOS}$	Mean: μ_{SOS} Variance: σ^2_{SOS}
Observational	Not permitted by design	Mean: μ^h_{SOS} Variance: $\sigma^{2h}_{SOS} + \boldsymbol{\sigma^2_0}$

5.2 STATISTICAL HYPOTHESES:

Non-inferiority of PCI at sites without SOS is hypothesized for both the effectiveness and safety endpoints.

Effectiveness Endpoint: μ_X = fraction in group X (all-cause mortality, MI, repeat coronary revascularization, or stroke at 12 months from PCI)

Null Hypothesis: $\mu_{NON\text{-}SOS} - \mu_{SOS} \geq 0.03$

Alternative: $\mu_{NON\text{-}SOS} - \mu_{SOS} < 0.03$

Safety Endpoints: μ_X = fraction in group X (all-cause mortality, MI, repeat coronary revascularization, or stroke at 30-days from PCI)

Null Hypothesis: $\mu_{NON\text{-}SOS} - \mu_{SOS} \geq 0.02$

Alternative: $\mu_{NON\text{-}SOS} - \mu_{SOS} < 0.02$

Rejection of the Effectiveness Null hypothesis implies that elective angioplasty is not less inferior in sites without SOS while rejection of the Safety Null hypothesis implies that elective angioplasty is not less safe in sites without SOS.

5.3 ANALYTICAL STRATEGY:

All analyses will utilize intention to treat principles. A two sample-test of proportions using a large sample (normal) approximation will be employed. The estimate of the difference in outcomes between the non-SOS and SOS groups is

$$\bar{y}_{\text{Non-SOS}} - \frac{\bar{y}_{\text{SOS}} + w \times \bar{y}^{h}_{\text{SOS}}}{1 + w} \qquad (1)$$

Where :

$\bar{y}_{\text{Non-SOS}}$ = Mean outcome in the Non-SOS group

$\bar{y}_{\text{SOS}}$ = Mean Outcome in the randomized SOS group

$\bar{y}^{h}_{\text{SOS}}$ = Mean Outcome in the non-randomized SOS group

$$w = \frac{\sigma^2_{\text{SOS}}}{\sigma^{2h}_{\text{SOS}} + \sigma^2_0}$$

σ^2_{SOS} = Variance of mean outcome in the randomized SOS group

σ^{2h}_{SOS} = Variance of mean outcome in the non-randomized SOS group

σ^2_0 = Degree of bias in the non-randomized SOS group.

The variance of the estimate in Equation 1 is given by:

$$\sigma^2_{\text{Non-SOS}} + \left(\frac{1}{\sigma^2_{\text{SOS}}} + \frac{1}{\sigma^{2h}_{\text{SOS}} + \sigma^2_0} \right)^{-1}.$$

The value of σ^2_0 is specified a-priori as it denotes prior opinion regarding the potential extent of the bias between the non-randomized and randomized SOS groups. A value of $\sigma^2_0 = 0$ implies that there is no bias and larger values correspond to more bias.[1] We have chosen $\sigma^2_0 = 1.02$ ($\sigma^2_0 = 1.04$) that results by assuming that the non-randomized SOS group may over- or under-estimate the MACE rate in the randomized SOS group by a factor of 2, e.g.,

$$1.96 \times \sigma_0 = 2 \text{ iff } \sigma_0 = 1.02.$$

1The value of this variance component will change if the outcome is tranformed as σ_0 is measured in units of y.

5.4 SAMPLE SIZE CONSIDERATIONS:

Sample size was computed assuming 90% power, an overall experiment-wise Type I error rate of 0.05 (0.025 for effectiveness and 0.025 for safety), and a two-sample test of proportions[7]. The effectiveness effect size of 3% was selected assuming 30% of a 10.0% 12 month composite base rate and a safety effect size of 2.0% was selected assuming 50% of a 30-day composite base rate of 4%. Using a 3:1 randomization scheme a total of 6000 patients will participate in the study: 3600 patients will be randomized to NON-SOS sites and 2400 will comprise the SOS group (1200 of which will be randomized from NON-SOS sites to SOS sites and 1200 of which will be selected from SOS sites).

Required total sample size assuming 90% power, Type I error of 0.025, $\mu_{NON\text{-}SOS} - \mu_{SOS} \geq \delta$ versus $\mu_{NON\text{-}SOS} - \mu_{SOS} < \delta$.			
12 month Effectiveness Composite Endpoint (%)	Randomization Ratio: NON-SOS to SOS		
	3:1	2:1	1:1
9.0 ($\delta = 2.7$)	6296	5313	4722
10.0 ($\delta = 3.0$)	5604	4729	4203
11.0 ($\delta = 3.3$)	5038	4251	3779
30-Day Safety Composite Endpoint (%)	Randomization Ratio: NON-SOS to SOS		
	3:1	2:1	1:1
3.0 ($\delta = 1.5$)	7248	6116	5436
4.0 ($\delta = 2.0$)	5380	4540	4035
5.0 ($\delta = 2.5$)	4260	3594	3195

[7] These calculations were derived using a two group test of equivalence in proportions using large unequal sample sizes; they ignore the additional component σ^2_0. Thus the sample sizes are inflated to reflect the extra variation.

6.0 DEFINITIONS

ABRUPT CLOSURE

Abrupt Closure. Defined as the occurrence of new (during the index procedure) severely reduced flow (TIMI grade 0-2) within the target vessel that persisted and required rescue by stenting or other treatment, or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application does reverse the closure.

Subabrupt Closure. Defined as abrupt closure that occurred after the index procedure is completed (and the subject left the catheterization laboratory) and before the 30-day follow-up endpoint.

Threatened Abrupt Closure. Defined as a grade B dissection and ≥ 50% diameter stenosis or any dissection of grade C or higher.

APPROPRIATENESS OF REVASCULARIZATION

Defined as the proportion of lesions meeting Class I and II criteria per the AHA/ACC/SCAI 2005 Guideline Update for PCI (see, Manual of Operations) or subsequent modifications thereof.

COMPLETENESS OF REVASCULARIZATION

Defined as proportion of epicardial vessels with >70% and <100% stenosis treated with procedural success.

BLEEDING COMPLICATIONS

Defined as a procedure related hemorrhagic event that requires a transfusion or surgical repair.

CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION (CCS)

Class I Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Class II Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the first hours after awakening. Angina if walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III Marked limitations of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

Class IV Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.

DE NOVO LESION
Defined as a native coronary artery lesion not previously treated.

DEATH
Death is divided into 2 categories:

Cardiac death is defined as death due to any of the following:

1. Acute myocardial infarction.
2. Cardiac perforation/pericardial tamponade.
3. Arrhythmia or conduction abnormality.
4. Stroke within 30 days of the procedure or stroke suspected of being related to the procedure.
5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
6. Any death in which a cardiac cause cannot be excluded.

Non-cardiac death is defined as a death not due to cardiac causes (as defined above).

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute)
CLASSIFICATION

Type A Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.

Type E Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F Filling defect accompanied by total coronary occlusion.

DISTAL EMBOLIZATION
Defined as a new abrupt cut off of contrast column or filling defect distal to the treated lesion.

EMERGENT REVASCULARIZATION
Defined as repeat percutaneous coronary intervention or coronary bypass surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

INCOMPLETE APPOSITION
Failure of the stent to completely appose to the vessel wall after placement is defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut in the ultrasound image.

LESION CLASS (American College of Cardiology/American Heart Association Class)

Type A Lesions: Minimally complex, discrete (length <10 mm), concentric, readily accessible, non angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.

Type B Lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

Type C Lesions: Severely complex, diffuse (length >2 cm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions**.**

LESION SUCCESS
Attainment of < 20 % residual stenosis of the target lesion using any percutaneous method.

MAJOR ADVERSE CARDIAC EVENT (MACE)
Defined as a composite endpoint of all cause mortality, target vessel myocardial infarction (Q wave and non-Q wave), repeat coronary revascularization of target vessel or non-target vessel (PTCA or CABG), or stroke.

MAJOR VASCULAR COMPLICATION
Defined as the occurrence of any of the following as a result of the index procedure:

1. Hematoma at access site >5 cm
2. False aneurysm
3. AV fistula
4. Retroperitoneal bleed
5. Peripheral ischemia/nerve injury
6. Procedure related transfusion
7. Vascular surgical repair or ultrasound compression required

MINIMAL LUMINAL DIAMETER (MLD)
Defined as the mean minimum lumen diameter derived (by the quantitative coronary angiography laboratory) from the average of two orthogonal views (when possible) of the narrowest point within the area of assessment - in lesion, in stent or in segment.

MYOCARDIAL INFARCTION
A positive diagnosis of myocardial infarction of the target vessel is made when one of the following criteria is met:

1. **Q wave MI:** (QMI) will require one of the following criteria:
   1.1. Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by independent review of the CEC, in the absence of timely cardiac enzyme data.

   1.2. New pathologic Q waves in two or more contiguous ECG leads as determined by independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.

2. **Non-Q Wave MI (NQWMI):** for this trial NQWMI will be defined using the following definitions:

   2.1. FDA Definition:
   Elevated CK $\geq$ 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves

   2.2. Additional Definition:
   Elevation of post-procedure CK-MB levels to $\geq$3 times normal.

NO REFLOW
Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERFORATION
Perforations will be classified as follows:
Angiographic perforation: perforation detected by the clinical site or the core laboratory at any point during the procedure.
Clinical perforation: perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death.
Pericardial hemorrhage/tamponade: perforation resulting in cardiac tamponade.

PROCEDURAL SUCCESS
Attainment of <20 % residual stenosis of the target lesion and no occurrence of in-hospital MACE.

REINFARCTION
Defined as once a downward trend in cardiac enzymes (CK-MB) from index event is noted, any increase in CK-MBs 50% above prior nadir.

RESTENOTIC LESION
Defined as a lesion in a vessel segment that has undergone prior percutaneous treatment without stent placement.

REFERENCE VESSEL DIAMETER (RVD)
Defined as the average diameter of normal segments within 10 mm proximal and distal to the target lesion from 2 orthogonal views using QCA.

STENT THROMBOSIS
Defined as angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain and ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

STROKE
Stroke is defined as a neurological deficit lasting more than 24 hours with a brain imaging study (if performed) showing infarction or hemorrhage.

TARGET LESION REVASCULARIZATION (TLR)
Defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

Ischemia driven (e.g.,clinically-driven) revascularizations are those in which the subject has a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms. Revascularization of a target lesion with an in-lesion diameter stenosis ≥70% (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically-driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms.

Non-clinically driven repeat target lesion revascularizations are those in which the subject undergoes a non-emergent revascularization for a diameter stenosis <50% (by QCA). Non-emergent repeat target lesion revascularization for a diameter stenosis <70% (by QCA) in subjects without either a positive functional study or angina are also considered non-clinically driven. Defined as any repeat revascularization of the target site whether by PCI or bypass surgery.

TARGET VESSEL FAILURE (TVF)
Defined as a composite of target vessel revascularization (defined below), Q or Non Q-wave myocardial infarction, or cardiac death that could not be clearly attributed to a vessel other than the target vessel.

Target vessel failure is a more conservative and broader category than MACE and includes any target vessel revascularization as well as any MI or any cardiac death that cannot be clearly attributed to a non-target vessel. Target vessel failure, thus, includes any revascularization or adverse endpoint due to re-narrowing of any portion of the target vessel, and assumes that the entire vessel is vulnerable to late failures because of guide catheter or guide wire trauma or progression of disease remote from the treatment site.

Target vessel failure will be reported when any of the following events occur:

- MI occurs in territory not clearly other than that of the target vessel.
- Cardiac death not clearly due to a non-target vessel endpoint.
- Target vessel revascularization is determined.

TARGET VESSEL REVASCULARIZATION (TVR)
Defined as any repeat percutaneous intervention of the target vessel whether PCI or bypass surgery. Ischemia-driven TVR is defined the same as above for TLR.

TIMI CLASSIFICATION
TIMI 0 No perfusion.
TIMI 1 Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.

TIMI 2 Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.

TIMI 3 Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

7.0 ENDPOINT DATA COLLECTION AND STUDY ENDPOINTS

7.1. CLINICAL FOLLOW-UP

A clinical follow-up office visit will be scheduled at 30 days + 7 days and at 12 months ± 30 days post-procedure for all patients. Clinical follow-up for determination of study endpoints is required for ischemia-driven revascularization of the target vessel (TVR), target lesion (TLR), non-target vessel (non-TVR), and major adverse cardiac events (see endpoints below).

In a subset of consecutive patients (N=600) angiographic films will be submitted for analysis performed by a blinded core laboratory, to assess baseline angiographic characteristics, pre- and post-procedure lesion characteristics, completeness and appropriateness of revascularization.

7.2 PRIMARY ENDPOINT

The primary endpoint of this trial will be measured at 30 days (safety) and 12 months (efficacy). The primary endpoint is defined as the occurrence of death (from all cause), myocardial infarction, repeat coronary revascularization, or stroke.

7.3 SECONDARY ENDPOINTS

The secondary endpoints include both safety and efficacy measures and are as follows:

1. All cause mortality at 30 days and 12 months.
2. Stroke at 30 days and 12 months.
3. Ischemia driven TLR and TVR at 12 months.
4. Any coronary revascularization through month 12. Revascularization will be categorized according to relatedness to the target lesion or target vessel (e.g., as either target lesion or target vessel related or non-target lesion or non-target vessel related).
5. Rate of emergent revascularization through day 30.
6. Procedure success defined as lesion success without the occurrence of in-hospital MACE.
7. Major vascular complications, including access site complications and major bleeding events requiring transfusions, through day 30.
8. Completeness of revascularization, defined as proportion of epicardial vessels with >70% and <100% stenosis treated with procedural success.
9. Appropriateness of revascularization, defined as the proportion of lesions meeting Class I and II criteria per the 2005 Angioplasty Guidelines of AHA/ACC/SCAI or subsequent modifications thereof.

8.0 DATA SUBMISSION REQUIREMENTS

8.1 REQUIRED DATA

All required data for this trial will be collected via electronic case report forms (eCRF) and securely transferred by a 21 CFR Part 11 compliant electronic data capture (EDC) system.

8.2 DATA COLLECTION

Electronic Case Report Form Development, Modification and Maintenance: The final set of eCRFs is designed to accommodate the specific features of the trial design. Modification of eCRFs will only be made if deemed necessary by the Executive Operations Committee.

Components of the eCRF:

1. Baseline subject demographic and clinical data.
2. Procedure data (including stents used, procedural complications and drugs used during and after the procedure).
3. Hospital Discharge data (including post-procedural complications, ischemic or vascular complications, in-hospital major events, and pertinent laboratory tests).
4. Study endpoint event data.
5. Clinical event follow-up data related to study endpoints (includes incidence and timing of any ischemic or major clinical event from hospital discharge to study completion, such as death, MI, stroke or revascularization by a percutaneous procedure or CABG and indication of target vessel involvement).

8.3 DATA COLLECTION AND TRACKING

Research coordinators at each clinical site will perform primary data collection drawn from source document (hospital chart) reviews. Data will be entered by the site personnel into eCRFs on the internet-based EDC system. This will ensure data are forwarded to HCRI in an expedited fashion. HCRI will provide clinical monitoring, including review of EDC data with verification to the source documentation. This will include operator worksheets retained with eCRF documentation and hospital charts.

In the initial phase of the protocol, periodic teleconference calls between the Executive Operations Committee, HCRI and each clinical site may be performed to resolve any problems concerning the protocol and data collection. Periodic recruitment status reports generated by the EDC system will identify variations in recruitment frequency among sites.

8.4 TIME WINDOWS FOR EXPECTED COMPLETION OF ELECTRONIC CASE REPORT FORMS/REPORTS

The eCRF data submission detailed in the following table should be completed as follows:

Table 4: Responsibilities for Submitting eCRFs

Type of eCRF	Prepared by Investigator For	Time of Notification
Subject Enrollment eCRF	HCRI	Within 24 hours of enrollment
Baseline eCRF	HCRI	Within 7 days of enrollment
Hospital Discharge Form eCRF	HCRI	Within 7 days of discharge
Clinical Follow-up eCRFs	HCRI	Within 7 days of subject visit
Study Endpoint Notification eCRF	HCRI, IRB	Within 7 days hours of knowledge of event
Study Exit Form	HCRI	Within 7 days hours of subject visit

Other data and reports detailed in the following table should be submitted (by fax, mail, or overnight courier, if necessary) to HCRI, the Executive Operations Committee (via HCRI) or the IRB as follows:

Table 5: Responsibilities for Submitting Reports and Other Data

Type of Report	Prepared by Investigator For	Time of Notification
Screening Logs	HCRI	Submit to HCRI weekly
Informed consent not obtained from subject	Executive Operations Committee (via HCRI), IRB	Within 5 working days of index procedure
Subject death during the investigation	Executive Operations Committee, HCRI and IRB	Within 1 day of knowledge of event
Withdrawal of IRB approval	Executive Operations Committee, HCRI	Within 5 days of withdrawal
Annual reports	Submit to IRB	Annually
Final report	IRB	Within 3 months of study completion or termination

9.0 STUDY RESPONSIBILITIES

9.1 INVESTIGATOR RESPONSIBILITY FOR STUDY CONDUCT

Study investigators will ensure that all work and services they provide will be conducted in compliance with the standards of good clinical and research practice. It is the responsibility of each study-site principal investigator to provide the current study protocol to all sub-investigators and other staff responsible for study conduct, as well as provide for the training of all sub-investigators or other staff involved in the conduct of this research.

Upon completion of the trial, the principal investigator will submit a final written report to the reviewing Institutional Review Board within three (3) months of completion or termination.

9.2 SELECTION AND MONITORING OF CLINICAL SITES AND OPERATORS

In the selection of study investigators, the Massachusetts Department of Public Health (MDPH) requires each interventionalist to have adequate experience with percutaneous coronary interventional devices, demonstrate commitment to patient safety and consistency in adherence to study protocols. The MDPH will closely monitor compliance with the protocol throughout the study.

Each study site will be subject to on-going monitoring. Study sites will be evaluated for meeting enrollment criteria and for the accurate and timely submission of data forms, catheterization or surgical reports (as requested for event adjudication) and timely response to data queries from the study monitors or data coordinating center.

9.3 STUDY CLOSEOUT

Upon completion of the clinical study (when all subjects enrolled have completed the follow up visits and the eCRFs and queries have been completed) a study closure visit will be performed. The Monitor will ensure that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussing retention of study files, possibility of site audits, publication policy, and to ensure that the investigator will notify the local IRB regarding study closure.

9.4 AUDITS/INSPECTIONS

In the event that audits are initiated by the sponsors or its delegate or local regulatory authority, the investigator shall allow access to the original medical records and provide all requested information.

9.5 PUBLICATION POLICIES

At the conclusion of the study, a multi-center publication will be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of the Executive Operations Committee and/or MA-DPH. The analysis of other pre-specified and non pre-specified endpoints will be performed at HCRI. Such analyses, as well as other proposed investigations by members of the Steering Committee, will require the approval of the Executive Operations Committee. Several secondary manuscripts are anticipated with principal authorship drawn from members of the Steering Committee. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of the Executive Operations Committee and MA-DPH.

10.0 STUDY COMMITTEES

10.1 EXECUTIVE OPERATIONS COMMITTEE

The Executive Operations Committee will be responsible for the day-to-day administrative management of the trial. This committee will meet periodically (at least quarterly) by teleconference to monitor subject enrollment, clinical site progress, and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications proposed by members of the Steering Committee.

Alice Jacobs	Principal Investigator, BUMC
Laura Mauri	Co-PI, BWH, HCRI
Sharon-Lise Normand	MASS-DAC, Co-PI, HMS
Donald Cutlip	Clinical Event Adjudication, HCRI
Paul Dreyer	MA-DPH
TBD	SOS Hospital Representative
TBD	Non-SOS Hospital Representative

10.2 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee is made up of interventional and non-interventional cardiologists who are not participants in the study. The Clinical Events Committee is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study.

At the onset of the trial, the Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the primary results of the trial.

Once the specific criteria for clinical events and endpoints are established by the Clinical Events Committee, the Harvard Clinical Research Institute (HCRI) will be responsible for categorizing all clinical events when all necessary data are available.
The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is not available. The Committee will also review and rule on all deaths that occur throughout the trial.

10.3 DATA SAFETY MONITORING BOARD

The Data Safety Monitoring Board (DSMB) is composed of at least five members (four physicians from the fields of cardiology and interventional cardiology and one bio-statistician), who are not directly involved in the conduct of the trial. The DSMB will review the study on a periodic basis to be defined at their first meeting. The DSMB will meet twice yearly after approximately 1000, 2000, 3000, 4000, 5000 and 6000 subjects have been enrolled and have 30 day follow-up data available for review. The DSMB is empowered to call additional meetings or revise the interims by which data is reviewed.

Based on the safety data, the DSMB may recommend that the Executive Committee modify or stop the trial. All final decisions, however, regarding trial modifications, rest with the Executive Committee. No formal statistical rule for stopping the trial will be defined.

10.4 STEERING COMMITTEE

The Steering Committee consists of members of the Executive Operations Committee and all clinical site principal investigators.

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